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FILE CONTENT:1840 - 9 Mar 2008 VOL 148 ISS 11

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This file contains CAS Registry Numbers for easy and accurate substance
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L6              STR
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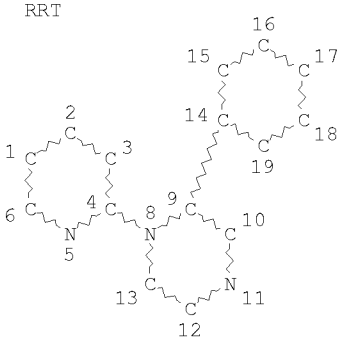
RRT



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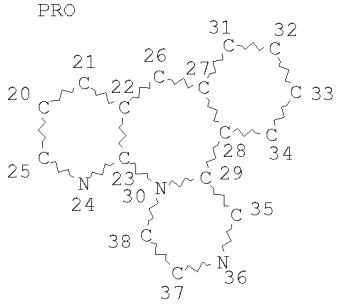

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  37

STEREO ATTRIBUTES: NONE
L8           13 SEA FILE=CASREACT SSS FUL L6 (    30 REACTIONS)

100.0% DONE      30 VERIFIED      30 HIT RXNS                      13 DOCS
SEARCH TIME: 00.00.01


=> d bib abs crd l13 tot
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L13 ANSWER 1 OF 1 CASREACT COPYRIGHT 2008 ACS on STN
AN 142:134623 CASREACT
TI Preparation of enantiomerically pure (S)-mirtazapine
IN Wieringa, Johannes Hubertus; Van De Ven, Adrianus Antonius Martinus; Kemperman, Gerardus Johannes
PA Akzo Nobel N.V., Neth.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2005005410	A1	20050120	2004WO-EP0051357	20040705
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	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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	CA-----2531165	A1	20050120	2004CA-002531165	20040705
	EP-----1656365	A1	20060517	2004EP-000741958	20040705
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	CN-----1820000	A	20060816	2004CN-080019489	20040705
	BR--2004012447	A	20060919	2004BR-000012447	20040705
	LT---------5382	B	20061127	2005LT-000000107	20051212
	NO--2005006175	A	20060123	2005NO-000006175	20051223
	US--2006229300	A1	20061012	2006US-000564193	20060106
	IN-2006CN00083	A	20070831	2006IN-CN0000083	20060106
	MX-2006PA00325	A	20060330	2006MX-PA0000325	20060109
	LV--------13441	B	20060820	2006LV-000000021	20060210
PRAI	2003EP-000102095		20030710		
	2004WO-EP0051357		20040705		

OS MARPAT 142:134623
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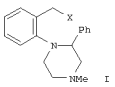
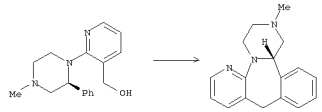


I

AB (S)-Mirtazapine was prepared using a ring closure reaction of (S)-pyridylpiperazine I (X = leaving group) using an acid and an organic solvent or in the absence of solvent. For example, (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine, I (X = OH), was dissolved in N-methylpyrrolidinone and polyphosphoric acid was added. The title compound was obtained in 68% yield with 99.2% ee.

L13 ANSWER 1 OF 1 CASREACT COPYRIGHT 2008 ACS on STN (Continued)

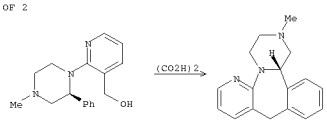
RX(1) OF 2



76%

NOTE: optimization study, stereoselective, polyphosphoric acid was used
CON: 18 hours, room temperature -> 130 deg C

RX(2) OF 2



84%

NOTE: stereoselective, polyphosphoric acid was used
CON: 18 hours, room temperature -> 130 deg C

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

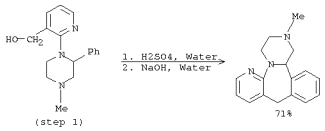
=> d bib abs crd l14 tot

L14 ANSWER 1 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
AN 143:7729 CASREACT
TI Preparation of mirtazapine antidepressant
IN Yang, Yushe; Guo, Baishu; Chen, Kaixian; Ji, Ruyun
PA Shanghai Institute of Pharmacy, Chinese Academy of Sciences, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 9 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI CN-----1429819	A	20030716	2001CN-000145561	20011229
PRAI 2001CN-000145561		20011229		

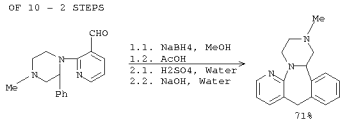
AB The method comprises substituting 1-methyl-3-phenylpiperazine with 2-chloro-3-cyanopyridine in DMF or DMSO to obtain 2-(3-cyano-2-pyridinyl)-4-methyl-2-phenylpiperazine, reducing with Raney Ni/NaH2PO2 in water-acetic acid-pyridine mixed solvent at 50-60° to obtain 2-(3-formyl-2-pyridinyl)-4-methyl-2-phenylpiperazine, reducing with NaBH4 or KBH4 in alc. at room temperature, cyclizing with concentrated H2SO4 at 50-60°, and recrystg. in petroleum ether-ethanol-water.

RX(4) OF 10



CON: STAGE(1) 1 hour, room temperature; 3 hours, 50 - 60 deg C
STAGE(2) 0 deg C, pH 10

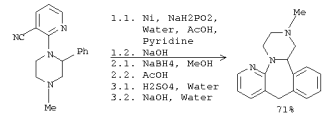
RX(7) OF 10 - 2 STEPS



CON: STEP(1.1) 2 hours, room temperature
STEP(2.1) 1 hour, room temperature; 3 hours, 50 - 60 deg C
STEP(2.2) 0 deg C, pH 10

L14 ANSWER 1 OF 7 CASREACT COPYRIGHT 2008 ACS on STN (Continued)

RX(9) OF 10 - 3 STEPS



CON: STEP(1.1) 5 hours, 50 - 60 deg C
STEP(1.2) pH 10
STEP(2.1) 2 hours, room temperature
STEP(3.1) 1 hour, room temperature; 3 hours, 50 - 60 deg C
STEP(3.2) 0 deg C, pH 10

L14 ANSWER 2 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
AN 138:304301 CASREACT
TI Novel synthesis and crystallization of piperazine ring-containing compounds such as mirtazapine
IN Singer, Claude; Liberman, Anita; Finkelstein, Nina
PA Israel
SO U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 552,485.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US--2003069417	A1	20030410	2002US-000206344	20020729
CN-----1679586	A	20051012	2005CN-010004288	20000418
CN-----1680374	A	20051012	2005CN-010004289	20000418
CN-----1680365	A	20051012	2005CN-010004290	20000418
US--2001051718	A1	20011213	2001US-000900646	20010706
US-----6545149	B2	20030408		
US--2003088094	A1	20030508	2002US-000283093	20021030
US-----6576764	B2	20030610		
US--2003120068	A1	20030626	2003US-000348757	20030123
US--2003135043	A1	20030717	2003US-000368441	20030220
US--2004176591	A1	20040909	2004US-000800918	20040316
AU--2005201117	A1	20050407	2005AU-000201117	20050315
PRAI 1999US-00130047P		19990419		
2000US-00182745P		20000216		
2000US-000552485		20000418		
2000AU-000043577		20000418		
2000CN-000807574		20000418		
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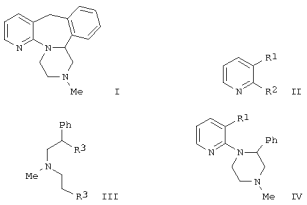
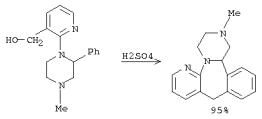
OS MARPAT 138:304301
GI



AB Mirtazapine (I) was prepared by reacting substituted pyridine II [R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2] with compound III [R3 = Cl, F, Br, I] followed by treating the resulting piperazine IV with ring closing reagent, such as H2SO4. The mirtazapine intermediate IV (R1 = CO2H) may be prepared by hydrolyzing IV (R1 = CN) with KOH at a temperature of at least about 140°C. New processes for recrystn. of I form crude mirtazapine are also disclosed. The present invention also relates to crystalline adducts of mirtazapine and water, preferably containing up to about 3.5% by weight water, pharmaceutical compns. containing the crystalline adducts, and methods of treating depression by administering such compns.

L14 ANSWER 2 OF 7 CASREACT COPYRIGHT 2008 ACS on STN (Continued)

RX(3) OF 4



NOTE: alternative prepn. gave lower yields
CON: 6 hours, 35 deg C

L14 ANSWER 3 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
AN 137:216962 CASREACT
TI Methods for the preparation of mirtazapine intermediates
IN Metzger, Leonid; Wizel, Shlomit
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2002070513	A1	20020912	2002WO-US0004340	20020214
	WO--2002070513	A9	20021121		
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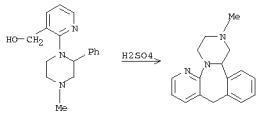
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA-----2438446	A1	20020214	2002CA-002438446	20020214
	AU--2002247130	A1	20020919	2002AU-000247130	20020214
	US--2002165238	A1	20021107	2002US-000073960	20020214
	US-----6774230	B2	20040810		
	EP-----1370549	A1	20031217	2002EP-000714893	20020214
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP--2005501808	T	20050120	2002JP-000569833	20020214
	IN-2003MN00777	A	20050429	2003IN-MN0000777	20030822
PRAI	2001US-00272699P		20010301		
	2002WO-US0004340		20020214		

AB The preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate (I) and other mirtazapine intermediates are described. These compds. are particularly useful in the preparation of mirtazapine. Thus, 1-(3-cyano-2-pyridyl)-4-methyl-2-phenylpiperazine was hydrolyzed with aqueous KOH, neutralized with HCl and the precipitate washed with water to give I whose crystal structure is reported.

RX(4) OF 7



NOTE: no exptl.

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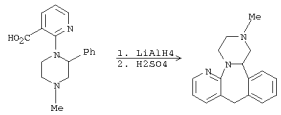
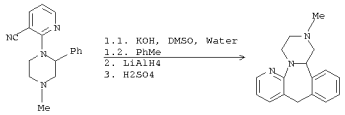


NOTE: 1) no exptl., 2) no exptl.

L14 ANSWER 3 OF 7 CASREACT COPYRIGHT 2008 ACS on STN (Continued)

RX(7) OF 7 - 3 STEPS



NOTE: 2) no exptl., 3) no exptl.

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 4 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
AN 136:401782 CASREACT
TI Process for the manufacture of anhydrous, solvent-free mirtazapine crystals
IN Maeda, Chiharu; Yoshikawa, Sadanobu; Iishi, Eiichi
PA Sumika Fine Chemicals Co., Ltd., Japan
SO Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP-----1209159	A2	20020529	2001EP-000111102	20010508
	EP-----1209159	A3	20030305		
	EP-----1209159	B1	20041117		
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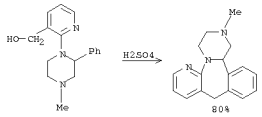
	US-----6660730	B2	20031209		
	AU--2001040301	A	20020606	2001AU-000040301	20010430
	AU------781974	B2	20050623		
	CA-----2346195	A1	20020527	2001CA-002346195	20010502
	AT------282616	T	20041215	2001AT-000111102	20010508
	PT-----1209159	T	20050131	2001PT-000111102	20010508
	ES-----2231340	T3	20050516	2001ES-000111102	20010508
	JP--2002220390	A	20020809	2001JP-000291863	20010925
PRAI	2000JP-000359891		20001127		

AB Methods for producing anhydrous mirtazapine crystals that are either (1) substantially free of lower alc. insolubles or (2) substantially free of residual solvent, and which have an average particle diameter of from 10-50 μm, are described where: one filters a lower alc. (e.g., methanol) solution of crude mirtazapine to provide a filtrate; concentrating the filtrate to provide a concentrated filtrate; and crystallizing the anhydrous mirtazapine from the concentrated filtrate using a precipitation solvent selected from heptane and petroleum ethers.

RX(1) OF 1



80%

L14 ANSWER 5 OF 7 CASREACT COPYRIGHT 2008 ACS on STN
AN 136:369741 CASREACT
TI A novel method for preparation of piperazine and its derivatives
IN Sebastian, Sonny; Patel, Hetal Virendra; Thennati, Rajamannar
PA Sun Pharmaceutical Industries Ltd., India
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2002038552	A1	20020516	2001WO-IN0000129	20010629
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	IN------190478	A1	20030802	2000IN-MU0000994	20001107
	AU--2001078669	A	20020521	2001AU-000078669	20010629
	BE------1013317	A6	20011106	2001BE-000000513	20010727
	CH-------692342	A5	20020515	2001CH-000001428	20010802
	US--2002095038	A1	20020718	2001US-000037309	20011025
	US------6603003	B2	20030805		
	IN-2002MU00411	A	20040228	2002IN-MU0000411	20020506
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OS	MARPAT 136:369741				

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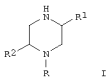
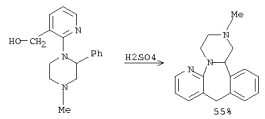


I

AB Compds. I [R = H, C1-6 alkyl, phenyl-C1-4 alkyl; R1 = H, Me, (un)substituted phenyl; R2 = H, Me, fluoromethyl] useful as starting materials for preparation of pharmaceutically active compds. are prepared by reacting R1COCO2R with H2NCH2CHR2NHR to give 3,4-dehydropiperazine-2-one and its derivs., followed by reacting with a reducing agent to yield I. Thus, 1-methyl-3-phenylpiperazine was prepared and used as starting material for preparation of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine.

RX(7) OF 28



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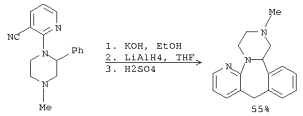
L14 ANSWER 5 OF 7 CASREACT COPYRIGHT 2008 ACS on STN (Continued)

RX(13) OF 28 - 2 STEPS

RX(21) OF 28 - 3 STEPS

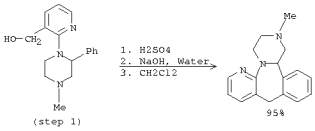


RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 7 CASREACT COPYRIGHT 2008 ACS on STN (Continued)

AB Mirtazapine, useful in treating depression (no data), was prepared by reacting pyridine I [R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2] with compound II [R3 = Cl, F, Br, I] followed by treating the resulting piperazine III with H2SO4. The mirtazapine intermediate 1-(3-carboxypyridly-2)-4-methyl-2-phenylpiperazine may be made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenylpiperazine with KOH at a temperature of at least about 130°C. The present invention also relates to new processes for recrystn. of mirtazapine form crude mirtazapine.

RX(1) OF 4



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 7 CASREACT COPYRIGHT 2008 ACS on STN

AN 133:321900 CASREACT

TI Novel synthesis and crystallization of piperazine ring-containing compounds such as mirtazapine

IN Singer, Claude; Liberman, Anita; Finkelstein, Nina

PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.

SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2000062782	A1	20001026	2000WO-US0010357	20000418
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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AU--2000043577	A	20001102	2000AU-000043577	20000418
AU------781221	B2	20050512		
TR---200103028	T2	20020121	2001TR-000003028	20000418
EP-----1178805	A1	20020213	2000EP-000923457	20000418
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HU--2002000839	A2	20020828	2002HU-000000839	20000418
HU--2002000839	A3	20030528		
JP--2004500324	T	20040108	2000JP-000611918	20000418
CN-----1679586	A	20051012	2005CN-010004288	20000418
CN-----1680374	A	20051012	2005CN-010004289	20000418
CN-----1680365	A	20051012	2005CN-010004290	20000418
ZA--2001008220	A	20021205	2001ZA-000008220	20011005
IN--2001MN001253	A	20050819	2001IN-MN0001253	20011011
HR--2001000747	A1	20021231	2001HR-000000747	20011015
US--2003088094	A1	20030508	2002US-000283093	20021030
US------6576764	B2	20030610		
US--2003120068	A1	20030626	2003US-000348757	20030123
US--2004176591	A1	20040909	2004US-000800918	20040316
AU--2005201117	A1	20050407	2005AU-000201117	20050315
IN-2005MN00621	A	20050923	2005IN-MN0000621	20050615

PRAI 1999US-00130047P 19990419
2000US-00182745P 20000216
2000AU-000043577 20000418
2000CN-000807574 20000418
2000US-000552485 20000418
2000WO-US0010357 20000418
2001US-000900646 20010706
2001IN-MN0001253 20011011
2002US-000283093 20021030
2003US-000368441 20030220

OS MARPAT 133:321900

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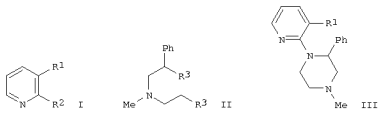


L14 ANSWER 7 OF 7 CASREACT COPYRIGHT 2008 ACS on STN

AN 112:139001 CASREACT

TI The synthesis of Org 3770 labeled with tritium, carbon-13 and carbon-14

AU Kaspersen, Frans M.; Van Rooij, Fons A. M.; Sperling, Eric G. M.; Wieringa, Joop H.

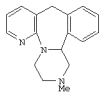
CS Sci. Dev. Group, Organon Int. BV, Oss, 5340 BH, Neth.

SO Journal of Labelled Compounds and Radiopharmaceuticals (1989), 27(9), 1055-68
CODEN: JLCRD4; ISSN: 0362-4803

DT Journal

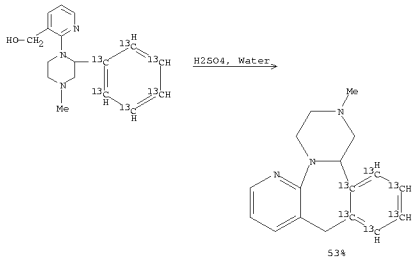
LA English

GI

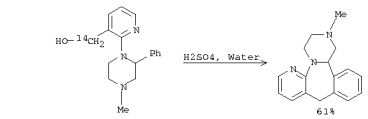


AB The syntheses of 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine (Org 3770, I) labeled with 3H (and 2H), 13C and 14C are described. Tritiated I was prepared either by exchange under alkaline conditions with tritiated water or catalytic reductive dehalogenation of a chloro analog with 3H2. 13C-labeled material was obtained in a 7-step synthesis starting from 13C-labeled benzene, whereas I-14C was prepared in a 3-step synthesis starting with 14CO2.

RX(10) OF 118

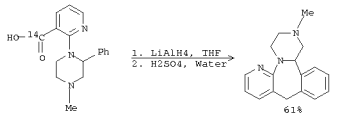


RX(15) OF 118

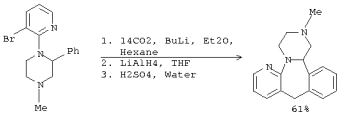


L14 ANSWER 7 OF 7 CASREACT COPYRIGHT 2008 ACS on STN (Continued)

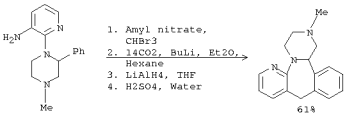
RX(30) OF 118 - 2 STEPS



RX(54) OF 118 - 3 STEPS



RX(55) OF 118 - 4 STEPS



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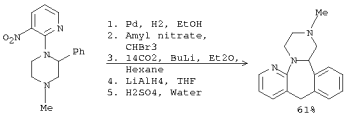

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DICTIONARY FILE UPDATES:  10 MAR 2008  HIGHEST RN 1007341-18-5

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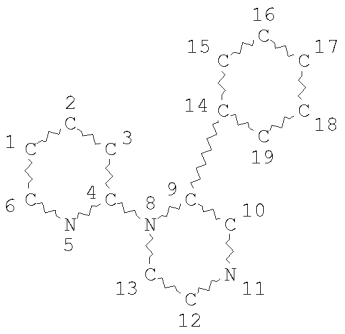


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DEFAULT ECLEVEL IS LIMITED

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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  18

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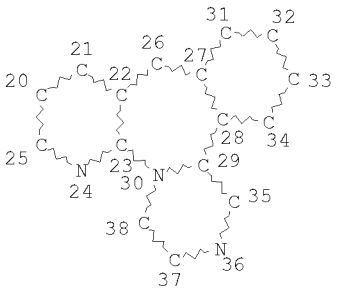

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DEFAULT ECLEVEL IS LIMITED

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FILE COVERS 1907 - 11 Mar 2008 VOL 148 ISS 11
FILE LAST UPDATED: 10 Mar 2008 (20080310/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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L26 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:55224 HCAPLUS
DN 142:134623
TI Preparation of enantiomerically pure (S)-mirtazapine
IN Wieringa, Johannes Hubertus; Van De Ven, Adrianus Antonius Martinus; Kemperman, Gerardus Johannes
PA Akzo Nobel N.V., Neth.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

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PI	WO--2005005410	A1	20050120	2004WO-EP051357	20040705
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	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU--2004255874	A1	20050120	2004AU-000255874	20040705
	CA-----2531165	A1	20050120	2004CA-002531165	20040705
	EP-----1656365	A1	20060517	2004EP-000741958	20040705
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
	CN-----1820000	A	20060816	2004CN-080019489	20040705
	BR--2004012447	A	20060919	2004BR-000012447	20040705
	LT--------5382	B	20061127	2005LT-000000107	20051212
	NO--2005006175	A	20060123	2005NO-000006175	20051223
	US--2006229300	A1	20061012	2006US-000564193	20060106 <--
	IN-2006CN00083	A	20070831	2006IN-CN0000083	20060106
	MX-2006PA00325	A	20060330	2006MX-PA0000325	20060109
	LV--------13441	B	20060820	2006LV-000000021	20060210
PRAI	2003EP-000102095	A	20030710		
	2004WO-EP051357	W	20040705		

OS CASREACT 142:134623; MARPAT 142:134623
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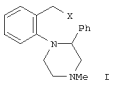


I

AB (S)-Mirtazapine was prepared using a ring closure reaction of (S)-pyridylpiperazine I (X = leaving group) using an acid and an organic solvent or in the absence of solvent. For example, (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine, I (X = OH), was dissolved in N-methylpyrrolidinone and polyphosphoric acid was added. The title compound was obtained in 68% yield with 99.2% ee.

IT 61337-87-9P, (S)-Mirtazapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(asym. synthesis of (S)-mirtazapine via acid-induced cyclization of (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine)

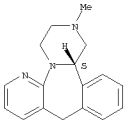
IT 824954-89-4 824954-90-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(asym. synthesis of (S)-mirtazapine via acid-induced cyclization of (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine)

IT 61337-87-9P, (S)-Mirtazapine

L26 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
RL: RCT (Reactant); RACT (Reactant or reagent);
PREP (Preparation)
(asym. synthesis of (S)-mirtazapine via acid-induced cyclization of (S)-1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine)

RN 61337-87-9 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



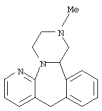
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d bib abs hitstr l28 tot

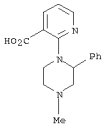
L28 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:460192 HCAPLUS
DN 143:133393
TI Preparation of 1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine
IN Zhang, Qingwen; Xu, Yanyan; Shi, Huilin
PA Shanghai Institute of Pharmaceutical Industry, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. given
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN-----1521166	A	20040818	2003CN-000115386	20030213 <--
PRAI 2003CN-000115386		20030213 <--		

OS CASREACT 143:133393
AB The title compound (I), an intermediate for the antidepressant mirtazapine, is prepared by reduction of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine (II) with diborane in ethers. Thus, reduction of II with NaBH4 and HCl in ethylene glycol di-Me ether at 60° for 2 h gave 89% I.
IT 85650-52-8P, Mirtazapine
RL: PNU (Preparation, unclassified); PREP (Preparation)
(preparation of 1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)

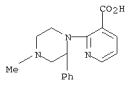


IT 61338-13-4 343626-55-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 1-(3-hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine)
RN 61338-13-4 HCAPLUS
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RN 343626-55-1 HCAPLUS
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)-, potassium salt (9CI) (CA INDEX NAME)

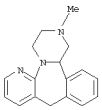
L28 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



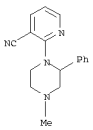
L28 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2005:436399 HCAPLUS
DN 143:7729
TI Preparation of mirtazapine antidepressant
IN Yang, Yushe; Guo, Baishu; Chen, Kaixian; Ji, Ruyun
PA Shanghai Institute of Pharmacy, Chinese Academy of Sciences, Peop. Rep. China
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 9 pp.
CODEN: CNXXEV
DT Patent
LA Chinese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN-----1429819	A	20030716	2001CN-000145561	20011229 <--
PRAI 2001CN-000145561		20011229 <--		

OS CASREACT 143:7729
AB The method comprises substituting 1-methyl-3-phenylpiperazine with 2-chloro-3-cyanopyridine in DMF or DMSO to obtain 2-(3-cyano-2-pyridinyl)-4-methyl-2-phenylpiperazine, reducing with Raney Ni/NaH2PO2 in water-acetic acid-pyridine mixed solvent at 50-60° to obtain 2-(3-formyl-2-pyridinyl)-4-methyl-2-phenylpiperazine, reducing with NaBH4 or KBH4 in alc. at room temperature, cyclizing with concentrated H2SO4 at 50-60°, and recrystg. in petroleum ether-ethanol-water.
IT 85650-52-8P, Mirtazapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of mirtazapine antidepressant)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)

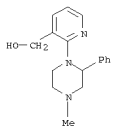


IT 61337-88-0P 61337-89-1P 852524-23-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of mirtazapine antidepressant)
RN 61337-88-0 HCAPLUS
CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

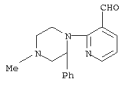


RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

L28 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



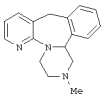
RN 852524-23-3 HCAPLUS
CN 3-Pyridinecarboxaldehyde, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



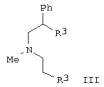
L28 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2003:282146 HCAPLUS
DN 138:304301
TI Novel synthesis and crystallization of piperazine ring-containing compounds such as mirtazapine
IN Singer, Claude; Liberman, Anita; Finkelstein, Nina
PA Israel
SO U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 552,485.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US--2003069417	A1	20030410	2002US-000206344	20020729 <--
CN-----1679586	A	20051012	2005CN-010004288	20000418 <--
CN-----1680374	A	20051012	2005CN-010004289	20000418 <--
CN-----1680365	A	20051012	2005CN-010004290	20000418 <--
US--2001051718	A1	20011213	2001US-000900646	20010706 <--
US-----6545149	B2	20030408		
US--2003088094	A1	20030508	2002US-000283093	20021030 <--
US-----6576764	B2	20030610		
US--2003120068	A1	20030626	2003US-000348757	20030123 <--
US--2003135043	A1	20030717	2003US-000368441	20030220 <--
US--2004176591	A1	20040909	2004US-000800918	20040316 <--
AU--2005201117	A1	20050407	2005AU-000201117	20050315 <--
PRAI 1999US-00130047P	P	19990419	<--	
2000US-00182745P	P	20000216	<--	
2000US-000552485	A2	20000418	<--	
2000AU-000043577	A3	20000418	<--	
2000CN-000807574	A3	20000418	<--	
2001US-000900646	A3	20010706	<--	
2002US-000283093	A3	20021030	<--	
2003US-000368441	B1	20030220	<--	

OS CASREACT 138:304301; MARPAT 138:304301
GI


I

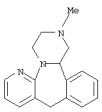

II


III

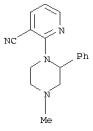

IV

AB Mirtazapine (I) was prepared by reacting substituted pyridine II [R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2] with compound III [R3 = Cl, F, Br, I] followed by treating the resulting piperazine IV with ring closing reagent, such as H2SO4. The mirtazapine intermediate IV (R1 = CO2H) may be prepared by hydrolyzing IV (R1 = CN) with KOH at a temperature of at least about 140°C. New processes for recrystn. of I form crude mirtazapine are also disclosed. The present invention also relates to crystalline adducts of mirtazapine and water, preferably containing up to about 3.5% by weight water, pharmaceutical compns. containing the crystalline adducts, and methods of treating depression by administering such compns.
IT 341512-90-1P

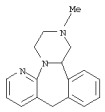
L28 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
mirtazapine)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



IT 61337-88-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and crystallization of piperazine ring-containing compds. such as mirtazapine)
RN 61337-88-0 HCAPLUS
CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

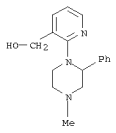


L28 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and crystn. of mirtazapine water adduct)
RN 341512-90-1 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, hydrate (9CI) (CA INDEX NAME)

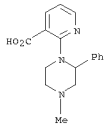


●x H2O

IT 61337-89-1P 61338-13-4P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and crystallization of piperazine ring-containing compds. such as mirtazapine)
RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RN 61338-13-4 HCAPLUS
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

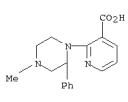


IT 85650-52-8P, Mirtazapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and crystallization of piperazine ring-containing compds. such as

L28 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:695977 HCAPLUS
DN 137:216962
TI Methods for the preparation of mirtazapine intermediates
IN Metzger, Leonid; Wizel, Shlomit
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 12 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2002070513	A1	20020912	2002WO-US0004340	20020214 <--
WO--2002070513	A9	20021121		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW			
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA-----2438446	A1	20020214	2002CA-002438446	20020214 <--
AU--2002247130	A1	20020919	2002AU-000247130	20020214 <--
US--2002165238	A1	20021107	2002US-000073960	20020214 <--
US-----6774230	B2	20040810		
EP-----1370549	A1	20031217	2002EP-000714893	20020214 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP--2005501808	T	20050120	2002JP-000569833	20020214 <--
IN-2003MN00777	A	20050429	2003IN-MN0000777	20030822 <--
PRAI 2001US-002726990P	P	20010301	<--	
2002WO-US0004340	W	20020214	<--	

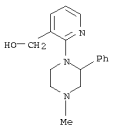
OS CASREACT 137:216962
AB The preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate (I) and other mirtazapine intermediates are described. These compds. are particularly useful in the preparation of mirtazapine. Thus, 1-(3-cyano-2-pyridyl)-4-methyl-2-phenylpiperazine was hydrolyzed with aqueous KOH, neutralized with HCl and the precipitate washed with water to give I whose crystal structure is reported.
IT 457601-25-1P, 1-(3-Carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate
RL: IMF (Industrial manufacture); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate as an intermediate for mirtazapine)
RN 457601-25-1 HCAPLUS
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)-, dihydrate (9CI) (CA INDEX NAME)



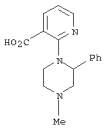
●2 H2O

IT 61337-89-1P, 1-(3-Hydroxymethyl-2-pyridyl)-4-methyl-2-phenylpiperazine 61338-13-4P, 1-(3-Carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate as an intermediate for mirtazapine)

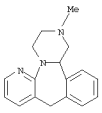
L28 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RN 61338-13-4 HCAPLUS
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

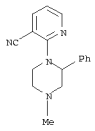


IT 85650-52-8P, Mirtazapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate as an intermediate for mirtazapine)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



IT 61337-88-0, 1-(3-Cyano-2-pyridyl)-4-methyl-2-phenylpiperazine
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of 1-(3-carboxy-2-pyridyl)-4-methyl-2-phenylpiperazine dihydrate as an intermediate for mirtazapine)
RN 61337-88-0 HCAPLUS
CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

L28 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)

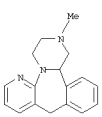


RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:406942 HCAPLUS
DN 136:401782
TI Process for the manufacture of anhydrous, solvent-free mirtazapine crystals
IN Maeda, Chiharu; Yoshikawa, Sadanobu; Iishi, Eiichi
PA Sumika Fine Chemicals Co., Ltd., Japan
SO Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

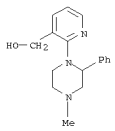
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP-----1209159	A2	20020529	2001EP-000111102	20010508 <--
EP-----1209159	A3	20030305		
EP-----1209159	B1	20041117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US--2002065413	A1	20020530	2001US-000842871	20010427 <--
US-----6660730	B2	20031209		
AU---2001040301	A	20020606	2001AU-000040301	20010430 <--
AU------781974	B2	20050623		
CA-----2346195	A1	20020527	2001CA-002346195	20010502 <--
AT-----282616	T	20041215	2001AT-000111102	20010508 <--
PT-----1209159	T	20050131	2001PT-000111102	20010508 <--
ES-----2231340	T3	20050516	2001ES-000111102	20010508 <--
JP--2002220390	A	20020809	2001JP-000291863	20010925 <--
PRAI 2000JP-000359891	A	20001127	<--	

OS CASREACT 136:401782
AB Methods for producing anhydrous mirtazapine crystals that are either (1) substantially free of lower alc. insolubles or (2) substantially free of residual solvent, and which have an average particle diameter of from 10-50 μm, are described where: one filters a lower alc. (e.g., methanol) solution of crude mirtazapine to provide a filtrate; concentrating the filtrate to provide a concentrated filtrate; and crystallizing the anhydrous mirtazapine from the concentrated filtrate using a precipitation solvent selected from heptane and petroleum ethers.
IT 85650-52-8P, Mirtazapine
RL: IMF (Industrial manufacture); PEP (Physical, engineering or chemical process); PRP (Properties); PUR (Purification or recovery); PYP (Physical process); PREP (Preparation); PROC (Process)
(process for the manufacture of anhydrous solvent-free mirtazapine crystals)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



IT 61337-89-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the manufacture of anhydrous solvent-free mirtazapine crystals)
RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

L28 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



L28 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2002:368461 HCAPLUS
DN 136:369741
TI A novel method for preparation of piperazine and its derivatives
IN Sebastian, Sonny; Patel, Hetal Virendra; Thennati, Rajamannar
PA Sun Pharmaceutical Industries Ltd., India
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2002038552	A1	20020516	2001WO-IN0000129	20010629 <--
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	IN------190478	A1	20030802	2000IN-MU0000994	20001107 <--
	AU---2001078669	A	20020521	2001AU-000078669	20010629 <--
	BE-----1013317	A6	20011106	2001BE-000000513	20010727 <--
	CH-------692342	A5	20020515	2001CH-000001428	20010802 <--
	US---2002095038	A1	20020718	2001US-000037309	20011025 <--
	US-----6603003	B2	20030805		
	IN-2002MU00411	A	20040228	2002IN-MU0000411	20020506 <--
PRAI	2000IN-MU0000994	A	20001107	<--	
	2001WO-IN0000129	W	20010629	<--	

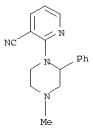
OS CASREACT 136:369741; MARPAT 136:369741
GI

I

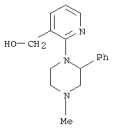
AB Compds. I [R = H, C1-6 alkyl, phenyl-C1-4 alkyl; R1 = H, Me, (un)substituted phenyl; R2 = H, Me, fluoromethyl] useful as starting materials for preparation of pharmaceutically active compds. are prepared by reacting R1COCO2R with H2NCH2CHR2NHR to give 3,4-dehydropiperazine-2-one and its derivs., followed by reacting with a reducing agent to yield I. Thus, 1-methyl-3-phenylpiperazine was prepared and used as starting material for preparation of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine.
IT 61337-88-0P 61337-89-1P 61338-13-4P
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of piperazine derivs. as starting materials for preparation of pharmaceutically active compds.)
RN 61337-88-0 HCAPLUS
CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

L28 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
ALL CITATIONS AVAILABLE IN THE RE FORMAT

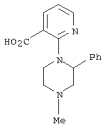
L28 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



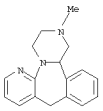
RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RN 61338-13-4 HCAPLUS
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



IT 85650-52-8P
RL: IMF (Industrial manufacture); PREP (Preparation)
(preparation of piperazine derivs. as starting materials for preparation of pharmaceutically active compds.)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

L28 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:435071 HCAPLUS
DN 135:33494
TI Process for the preparation of a pyridinemethanol compound
IN Iishi, Eiichi; Yoshikawa, Kanami
PA Sumika Fine Chemicals Co., Ltd., Japan
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2001042240	A1	20010614	2000WO-JP0006688	20000928 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	WO--2001042239	A1	20010614	2000WO-JP0005384	20000811 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA-----2394439	A1	20010614	2000CA-002394439	20000928 <--
	CA-----2394439	C	20070911		
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	AU------771484	B2	20040325		
	EP-----1238977	A1	20020911	2000EP-000962909	20000928 <--
	EP-----1238977	B1	20031126		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	AT------255103	T	20031215	2000AT-000962909	20000928 <--
	JP-----3930736	B2	20070613	2001JP-000543539	20000928 <--
PRAI	1999JP-000353514	A	19991213	<--	
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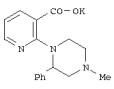
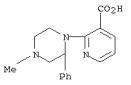
OS CASREACT 135:33494
GI



I

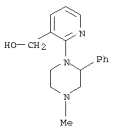
AB A pyridinemethanol compound useful as an important intermediate for the preparation of mirtazapine effective as an antidepressant can be prepared by reducing a potassium salt of pyridinecarboxylic acid as represented by formula I with a metal hydride. Thus, 1-butanol 162, KOH 60.93, and 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-carbonitrile oxalate 40 g were heated to give potassium 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-carboxylate, which was reduced in THF with 12.5 g lithium aluminum hydride to give 21.78 g 2-(4-methyl-2-phenylpiperazin-1-yl)pyridine-3-methanol (yield 70.78%).
IT 343626-55-1P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of pyridinemethanol compound as intermediate for mirtazapine)
RN 343626-55-1 HCAPLUS

L28 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)-, potassium salt (9CI) (CA INDEX NAME)

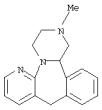


● K

IT 61337-89-1P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyridinemethanol compound as intermediate for mirtazapine)
RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



IT 85650-52-8P, Mirtazapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of pyridinemethanol compound as intermediate for mirtazapine)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)

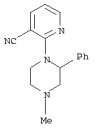


IT 331815-15-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of pyridinemethanol compound as intermediate for mirtazapine)
RN 331815-15-7 HCAPLUS
CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)-, ethanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 61337-88-0
CMF C17 H18 N4

L28 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



CM 2

CRN 144-62-7
CMF C2 H2 O4

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:435070 HCAPLUS
DN 135:33493
TI Process for the preparation of a pyridinemethanol compound
IN Iishi, Eiichi; Yoshikawa, Kanami
PA Sumika Fine Chemicals Co., Ltd., Japan
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2001042239	A1	20010614	2000WO-JP8005384	20000811 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU--2000064742	A	20010618	2000AU-000064742	20000811 <--
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CA-----2394439	C	20070911		
WO--2001042240	A1	20010614	2000WO-JP0006688	20000928 <--
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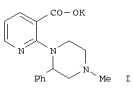
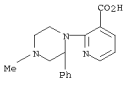
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU--2000074472	A	20010618	2000AU-000074472	20000928 <--
AU------771484	B2	20040325		
EP-----1238977	A1	20020911	2000EP-000962909	20000928 <--
EP-----1238977	B1	20031126		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
AT------255103	T	20031215	2000AT-000962909	20000928 <--
PT-----1238977	T	20040331	2000PT-000962909	20000928 <--
ES-----2209985	T3	20040701	2000ES-000962909	20000928 <--
JP-----3930736	B2	20070613	2001JP-000543539	20000928 <--
US-----6376668	B1	20020423	2000US-000706803	20001107 <--
US--2002035255	A1	20020321	2001US-000981919	20011019 <--
US-----6437120	B2	20020820		
PRAI 1999JP-000353514	A	19991213	<--	
2000WO-JP0005384	W	20000811	<--	
2000WO-JP0006688	W	20000928	<--	
2000US-000706803	A3	20001107	<--	

OS CASREACT 135:33493
GI



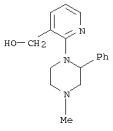
AB A pyridinemethanol compound serving as an important intermediate of mirtazapine useful as antidepressant can be prepared by reducing a potassium salt of a pyridinecarboxylic acid as represented by formula I with a metal hydride.
IT 343626-55-1P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of pyridinemethanol compound as intermediate for mirtazapine)

L28 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
RN 343626-55-1 HCAPLUS
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)-, potassium salt (9CI) (CA INDEX NAME)

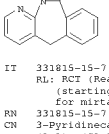


● K

IT 61337-89-1P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyridinemethanol compound as intermediate for mirtazapine)
RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



IT 85650-52-8P, Mirtazapine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(preparation of pyridinemethanol compound as intermediate for mirtazapine)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)

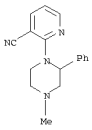


IT 331815-15-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; preparation of pyridinemethanol compound as intermediate for mirtazapine)
RN 331815-15-7 HCAPLUS
CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)-, ethanedioate (1:1) (CA INDEX NAME)

CM 1

CRN 61337-88-0
CMF C17 H18 N4

L28 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



CM 2

CRN 144-62-7
CMF C2 H2 O4

RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:396869 HCAPLUS
DN 135:12413
TI Anhydrous mirtazapine crystals and process for the production thereof
IN Iishi, Eiichi; Mamiya, Yoshiyuki
PA Sumika Fine Chemicals Co., Ltd., Japan
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2001038330	A1	20010531	2000WO-JP0006687	20000928 <--
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	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
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	W: AU, CA, IN, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
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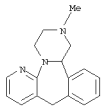
	CA-----2370376	A1	20010531		
	EP-----1225174	A1	20020724	2000EP-000962908	20000928 <--
	EP-----1225174	B1	20040317		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
	AT-----261966	T	20040415	2000AT-000962908	20000928 <--
	JP-----3699680	B2	20050928	2001JP-000540093	20000928 <--
PRAI	1999JP-000333049	A	19991124	<--	
	2000JP-000067476	A	20000310	<--	
	2000WO-JP0004835	W	20000719	<--	
	2000WO-JP0006687	W	20000928	<--	

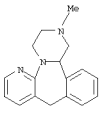
AB This document discloses : lowly hygroscopic anhydrous mirtazapine crystals exhibiting a moisture absorption of as low as 0.6 weight% (or below) when stored for 500 h in the air under the conditions of 25°C, relative humidity of 75% and atmospheric pressure; a process for the production of anhydrous mirtazapine crystals ; crystals of mirtazapine hydrates and a process for the production thereof. According to the process, stable anhydrous mirtazapine crystals exhibiting low hygroscopicity can be produced by a simple industrial method, and the obtained anhydrous mirtazapine crystals are suitably usable as an antidepressant by virtue of their extremely low hygroscopicity.
IT 341512-89-8P 341512-90-1P
RL: PEP (Physical, engineering or chemical process); PRP (Properties); SPN (Synthetic preparation); PREP (Preparation); PROC (Process)
(anhydrous mirtazapine crystals and process for production thereof)
RN 341512-89-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, hydrate (2:1) (CA INDEX NAME)



●1/2 H_2O

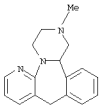
RN 341512-90-1 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-

L28 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
methyl-, hydrate (9CI) (CA INDEX NAME)

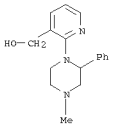


●x H_2O

IT 85650-52-8P, Mirtazapine
RL: PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(anhydrous mirtazapine crystals and process for production thereof)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



IT 61337-89-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(anhydrous mirtazapine crystals and process for production thereof)
RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2001:396868 HCAPLUS
DN 135:12412
TI Anhydrous mirtazapine crystals and process for producing the same
IN Iishi, Eiichi; Imamiya, Yoshiyuki
PA Sumika Fine Chemicals Co., Ltd., Japan
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO--2001038329	A1	20010531	2000WO-JP0004835	20000719 <--
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	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
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	CA-----2370376	C	20010531	2000CA-002370376	20000928 <--
	CA-----2370376	A1	20010531		
	WO--2001038330	A1	20010531	2000WO-JP0006687	20000928 <--
	W: AU, CA, IN, JP, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
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	AU------763502	B2	20030724		
	EP-----1225174	A1	20020724	2000EP-000962908	20000928 <--
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	PT-----1225174	T	20040531	2000PT-000962908	20000928 <--
	ES-----2214318	T3	20040916	2000ES-000962908	20000928 <--
	JP-----3699680	B2	20050928	2001JP-000540093	20000928 <--
	US--2002103372	A1	20020801	2002US-000041495	20020110 <--
	US-----6552189	B2	20030422		
	US--2003130504	A1	20030710	2003US-000337277	20030107 <--
	US-----6723845	B2	20040420		
	US--2004138447	A1	20040715	2003US-000743740	20031224 <--
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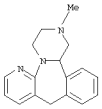
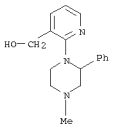
	2002US-000041495	A3	20020110	<--	
	2003US-000337277	A3	20030107	<--	

AB This document discloses : lowly-hygroscopic anhydrous mirtazapine crystals showing moisture absorption of 0.6 weight% or less when stored in the air at 25°C, at a relative humidity of 75% under atmospheric pressure for 500 h; a process for producing anhydrous mirtazapine crystals showing moisture absorption of 0.6 weight% or less when stored in the air at 25°C at a relative humidity of 75% under atmospheric pressure for 500 h characterized by drying crystals of mirtazapine hydrate; and a process for producing crystals of mirtazapine hydrate characterized by crystallizing crude mirtazapine by using a water soluble polar organic solvent and water. By using this production method, stable anhydrous mirtazapine having little hygroscopicity can be produced by a convenient industrial method. The anhydrous mirtazapine crystals are usable as active ingredients in an antidepressant.
IT 85650-52-8P, Mirtazapine
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of anhydrous mirtazapine crystals)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)

L28 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



IT 61337-89-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of anhydrous mirtazapine crystals)
RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 2000:756528 HCAPLUS
DN 133:321900
TI Novel synthesis and crystallization of piperazine ring-containing compounds such as mirtazapine
IN Singer, Claude; Liberman, Anita; Finkelstein, Nina
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals Usa, Inc.
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO--2000062782	A1	20001026	2000WO-US0010357	20000418 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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AU--2000043577	A	20001102	2000AU-000043577	20000418 <--
AU------781221	B2	20050512		
TR---200103028	T2	20020121	2001TR-000003028	20000418 <--
EP-----1178805	A1	20020213	2000EP-000923457	20000418 <--
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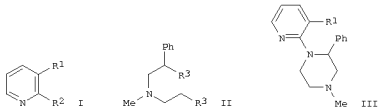
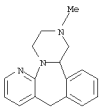
HU--2002000839	A2	20020828	2002HU-000000839	20000418 <--
HU--2002000839	A3	20030528		
JP--2004500324	T	20040108	2000JP-000611918	20000418 <--
CN-----1679586	A	20051012	2005CN-010004288	20000418 <--
CN-----1680374	A	20051012	2005CN-010004289	20000418 <--
CN-----1680365	A	20051012	2005CN-010004290	20000418 <--
ZA--2001008220	A	20021205	2001ZA-000008220	20011005 <--
IN-2001MN01253	A	20050819	2001IN-MN0001253	20011011 <--
HR--2001000747	A1	20021231	2001HR-000000747	20011015 <--
US--2003088094	A1	20030508	2002US-000283093	20021030 <--
US-----6576764	B2	20030610		
US--2003120068	A1	20030626	2003US-000348757	20030123 <--
US--2004176591	A1	20040909	2004US-000800918	20040316 <--
AU--2005201117	A1	20050407	2005AU-000201117	20050315 <--
IN-2005MN00621	A	20050923	2005IN-MN0000621	20050615 <--

PRAI 1999US-00130047P P 19990419 <--
2000US-00182745P P 20000216 <--
2000AU-000043577 A3 20000418 <--
2000CN-000807574 A3 20000418 <--
2000US-000552485 A3 20000418 <--
2000WO-US0010357 W 20000418 <--
2001US-000900646 A3 20010706 <--
2001IN-MN0001253 A3 20011011 <--
2002US-000283093 A3 20021030 <--
2003US-000368441 B1 20030220 <--
OS CASREACT 133:321900; MARPAT 133:321900
GI

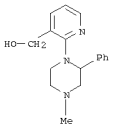


L28 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)

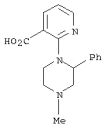
AB Mirtazapine, useful in treating depression (no data), was prepared by reacting pyridine I [R1 = CH2OH, CH2Cl, CH2Br, CH2I; R2 = NH2] with compound II [R3 = Cl, F, Br, I] followed by treating the resulting piperazine III with H2SO4. The mirtazapine intermediate 1-(3-carboxypyridly-2)-4-methyl-2-phenylpiperazine may be made by hydrolyzing 1-(3-cyanopyridyl-2)-4-methyl-2-phenylpiperazine with KOH at a temperature of at least about 130°C. The present invention also relates to new processes for recrystn. of mirtazapine form crude mirtazapine.
IT 85650-52-8P, Mirtazapine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation)
; USES (Uses)
(novel synthesis and crystallization of piperazine ring-containing compds. such as mirtazapine)
RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



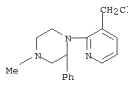
IT 61337-89-1P 61338-13-4P 303081-92-7P
303081-93-8P 303081-94-9P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(novel synthesis and crystallization of piperazine ring-containing compds. such as mirtazapine)
RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



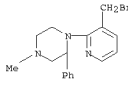
RN 61338-13-4 HCAPLUS
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



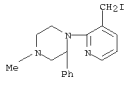
L28 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
RN 303081-92-7 HCAPLUS
CN Piperazine, 1-[3-(chloromethyl)-2-pyridinyl]-4-methyl-2-phenyl- (CA INDEX NAME)



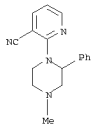
RN 303081-93-8 HCAPLUS
CN Piperazine, 1-[3-(bromomethyl)-2-pyridinyl]-4-methyl-2-phenyl- (CA INDEX NAME)



RN 303081-94-9 HCAPLUS
CN Piperazine, 1-[3-(iodomethyl)-2-pyridinyl]-4-methyl-2-phenyl- (CA INDEX NAME)

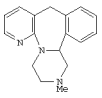


IT 61337-88-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(novel synthesis and crystallization of piperazine ring-containing compds. such as mirtazapine)
RN 61337-88-0 HCAPLUS
CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

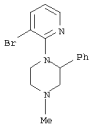
L28 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 1990:139001 HCAPLUS
DN 112:139001
TI The synthesis of Org 3770 labeled with tritium, carbon-13 and carbon-14
AU Kaspersen, Frans M.; Van Rooij, Fons A. M.; Sperling, Eric G. M.; Wieringa, Joop H.
CS Sci. Dev. Group, Organon Int. BV, Oss, 5340 BH, Neth.
SO Journal of Labelled Compounds and Radiopharmaceuticals (1989), 27(9), 1055-68
CODEN: JLCRD4; ISSN: 0362-4803
DT Journal
LA English
OS CASREACT 112:139001
GI



I

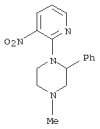
AB The syntheses of 1,2,3,4,10,14b-hexahydro-2-methylpyrazino[2,1-a]pyrido[2,3-c][2]benzazepine (Org 3770, I) labeled with 3H (and 2H), 13C and 14C are described. Tritiated I was prepared either by exchange under alkaline conditions with tritiated water or catalytic reductive dehalogenation of a chloro analog with 3H2. 13C-labeled material was obtained in a 7-step synthesis starting from 13C-labeled benzene, whereas I-14C was prepared in a 3-step synthesis starting with 14CO2.

IT 125967-24-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and carboxylation of)
RN 125967-24-0 HCAPLUS
CN Piperazine, 1-(3-bromo-2-pyridinyl)-4-methyl-2-phenyl- (CA INDEX NAME)

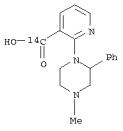


IT 125770-92-5P 125967-26-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and cyclization of)
RN 125770-92-5 HCAPLUS
CN 3-Pyridinemethanol, 2-[4-methyl-2-(phenyl-13C6)-1-piperazinyl]- (9CI) (CA INDEX NAME)

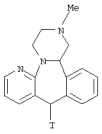
L28 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



IT 125967-25-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of)
RN 125967-25-1 HCAPLUS
CN 3-Pyridinecarboxylic-14C acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (9CI) (CA INDEX NAME)



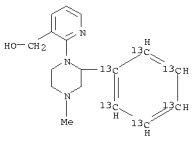
IT 109133-29-1P 125770-93-6P 125967-27-3P 125967-28-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 109133-29-1 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-10-t, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



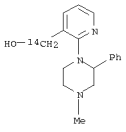
T

RN 125770-93-6 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-10a,11,12,13,14,14a-13C6, 1,2,3,4,10,14-hexahydro-2-methyl- (9CI) (CA INDEX NAME)

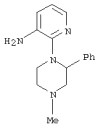
L28 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



RN 125967-26-2 HCAPLUS
CN 3-Pyridinemethanol-α-14C, 2-(4-methyl-2-phenyl-1-piperazinyl)- (9CI) (CA INDEX NAME)

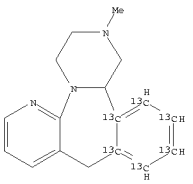


IT 125967-23-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and diazotization-bromination of)
RN 125967-23-9 HCAPLUS
CN 3-Pyridinamine, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

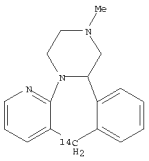


IT 125967-22-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrogenation of)
RN 125967-22-8 HCAPLUS
CN Piperazine, 4-methyl-1-(3-nitro-2-pyridinyl)-2-phenyl- (CA INDEX NAME)

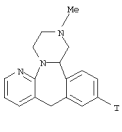
L28 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



RN 125967-27-3 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-10-14C, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



RN 125967-28-4 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-12-T, 1,2,3,4,10,14b-hexahydro-2-methyl- (9CI) (CA INDEX NAME)



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L28 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN
AN 1977:29883 HCAPLUS
DN 86:29883
OREF 86:4787a,4790a
TI Heterocyclic tetracyclic compounds
IN Van der Burg, Willem J.
PA AKZO N. V., Neth.
SO Ger. Offen., 40 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE-----2614406	A1	19761014	1976DE-002614406	19760402 <--
	DE-----2614406	C2	19920220		
	NL-----7504075	A	19761007	1975NL-000004075	19750405 <--
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	NL------189199	C	19930201		
	ZA-----7601756	A	19770330	1976ZA-000001756	19760323 <--
	AU-----7612361	A	19770929	1976AU-000012361	19760325 <--
	GB-----1543171	A	19790328	1976GB-000012270	19760326 <--
	CH-----622261	A5	19810331	1976CH-000003886	19760329 <--
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	DK------142498	C	19810706		
	FI-------62087	B	19820730	1976FI-000000884	19760401 <--
	FI-------62087	C	19821110		
	BE------840362	A1	19761004	1976BE-000165832	19760402 <--
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	SE------422941	C	19820715		
	JP-----51122099	A	19761025	1976JP-000037678	19760402 <--
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	FR-----2305986	A1	19761029	1976FR-000009686	19760402 <--
	FR-----2305986	B1	19800613		
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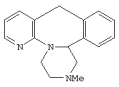
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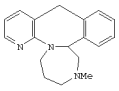
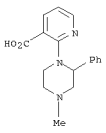

II

AB The title compds., e.g. I and II, with nervous system-depressant and antihistaminic activities (no data), are prepared by various procedures. Thus, reaction of 2-chloronicotinonitrile with 1-methyl-3-phenylpiperazine gives 2-(4-methyl-2-phenyl-1-piperazinyl)-3-pyridinecarbonitrile which is hydrolyzed to the carboxylic acid which is reduced to the hydroxymethyl derivative (III). Cyclization of 3.25 g III in concentrated H2SO4 at 20-35° gives after 2 hr and treatment with NH4OH 2.43 g I.

IT 61337-89-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and cyclization of)

RN 61337-89-1 HCAPLUS
CN 3-Pyridinemethanol, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

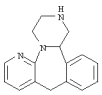


IT 61337-69-7P 61337-70-0P 61337-71-1P
61337-72-2P 61337-73-3P 61337-74-4P
61337-75-5P 61337-86-8P 61337-87-9P
61364-36-1P 61364-37-2P 85650-52-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 61337-69-7 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-, (2E)-2-butenedioate (9CI) (CA INDEX NAME)

CM 1

CRN 61337-68-6
CMF C16 H17 N3

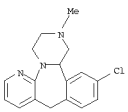


CM 2

CRN 110-16-7
CMF C4 H4 O4

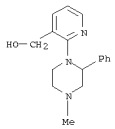
Double bond geometry as shown.

RN 61337-70-0 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 13-chloro-1,2,3,4,10,14b-hexahydro-2-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



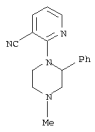
● 2 HCl

L28 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)



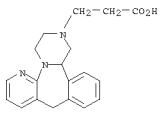
IT 61337-88-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)

RN 61337-88-0 HCAPLUS
CN 3-Pyridinecarbonitrile, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)



IT 61338-12-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and pyrolysis of)

RN 61338-12-3 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine-2(1H)-propanoic acid, 3,4,10,14b-tetrahydro- (CA INDEX NAME)

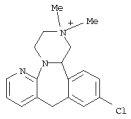


IT 61338-13-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of)

RN 61338-13-4 HCAPLUS
CN 3-Pyridinecarboxylic acid, 2-(4-methyl-2-phenyl-1-piperazinyl)- (CA INDEX NAME)

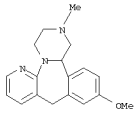
L28 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)

RN 61337-71-1 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepinium, 12-chloro-1,2,3,4,10,14b-hexahydro-2,2-dimethyl-, iodide (9CI) (CA INDEX NAME)

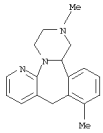


● I-

RN 61337-72-2 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-12-methoxy-2-methyl- (CA INDEX NAME)

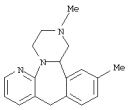


RN 61337-73-3 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2,11-dimethyl- (CA INDEX NAME)



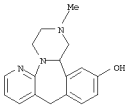
RN 61337-74-4 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2,13-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)

L28 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)

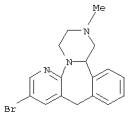


● HCl

RN 61337-75-5 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepin-13-ol, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)

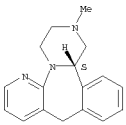


RN 61337-86-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 8-bromo-1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



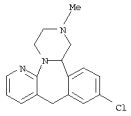
RN 61337-87-9 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bS)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 61364-36-1 HCAPLUS

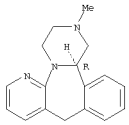
L28 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2008 ACS on STN (Continued)
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 12-chloro-1,2,3,4,10,14b-hexahydro-2-methyl-, dihydrochloride (9CI) (CA INDEX NAME)



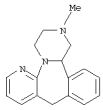
●2 HCl

RN 61364-37-2 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl-, (14bR)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 85650-52-8 HCAPLUS
CN Pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine, 1,2,3,4,10,14b-hexahydro-2-methyl- (CA INDEX NAME)



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     (FILE 'HCAPLUS' ENTERED AT 18:14:44 ON 11 MAR 2008)
               DEL HIS Y

     FILE 'HCAPLUS' ENTERED AT 19:20:44 ON 11 MAR 2008
L1             1 US20060229300/PN

     FILE 'REGISTRY' ENTERED AT 19:20:51 ON 11 MAR 2008

     FILE 'HCAPLUS' ENTERED AT 19:20:51 ON 11 MAR 2008
L2             TRA L1 1- RN :        3 TERMS

     FILE 'REGISTRY' ENTERED AT 19:20:51 ON 11 MAR 2008
L3             3 SEA L2

     FILE 'CASREACT' ENTERED AT 19:21:17 ON 11 MAR 2008
L4               STR
L5               STR L4
L6               STR L5
L7             0 L6
L8            13 L6 FULL
L9             8 L8 AND (PD<=20030710 OR AD<=20030710 OR PRD<=20030710)
L10            4 L8 AND PD<=20020710
L11            8 L9-10
L12            5 L8 NOT L11
                 SEL AN 2 L11
L13            1 E291 AND L11
L14            7 L11 NOT L13

     FILE 'REGISTRY' ENTERED AT 19:31:41 ON 11 MAR 2008
L15              STR L6
L16            0 L15
L17           34 L15 FULL
                 SAV TEM J193C1REG/A L17

     FILE 'CASREACT' ENTERED AT 19:33:06 ON 11 MAR 2008
                 SAV TEM J193C1CASRE/A L8

     FILE 'REGISTRY' ENTERED AT 19:33:13 ON 11 MAR 2008
L18              STR L6
L19            4 L18
L20          131 L18 FULL
                 SAV TEM J193C1REG2/A L20

     FILE 'HCAPLUS' ENTERED AT 19:34:04 ON 11 MAR 2008
L21           33 L17
L22          836 L20
L23           23 L21 (L) RACT+NT/RL
L24           56 L22 (L) (PREP+NT OR FORM+NT)/RL
L25           22 L23 AND L24
L26            1 L25 AND L1
L27           21 L25 NOT L26
L28           13 L27 AND (PD<=20030710 OR AD<=20030710 OR PRD<=20030710)
L29            8 L27 NOT L28

     FILE 'HCAOLD' ENTERED AT 19:38:23 ON 11 MAR 2008
L30            0 L17 AND L20
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